COLLAGENS

Collagens – OVERVIEW

- The collagen family of proteins plays an important role in maintaining the integrity of most tissues (including the skin).

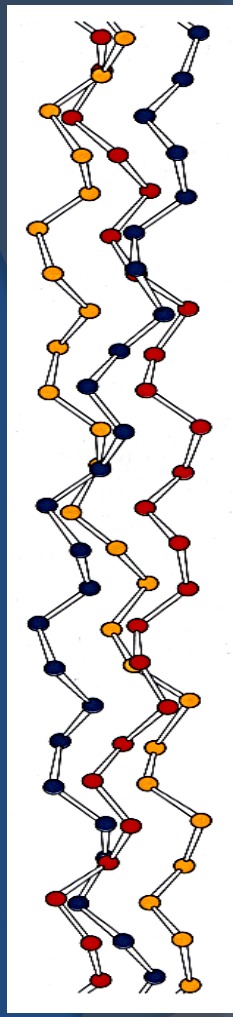
- This family currently includes 28 proteins that contain at least 43 distinct polypeptide chains, each encoded by a different gene

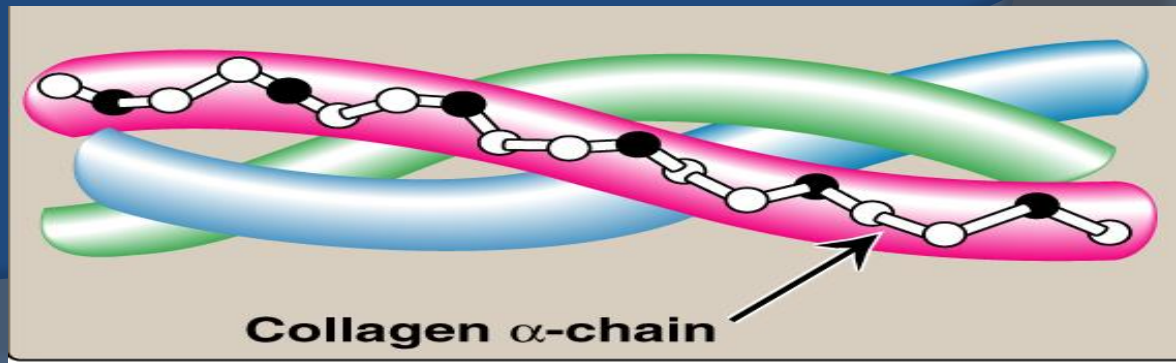
Collagens – OVERVIEW

- Collagens are examples of fibrous proteins.
- Collagen is the most abundant protein in the body.

Collagens –STRUCTURE

- All collagens consist of 3 polypeptide chains, known as α-chains, folded into a **triple helix**.
- In some collagens, the α-chains are identical (homotrimers), while others contain 2 or 3 different α-chains (heterotrimers)

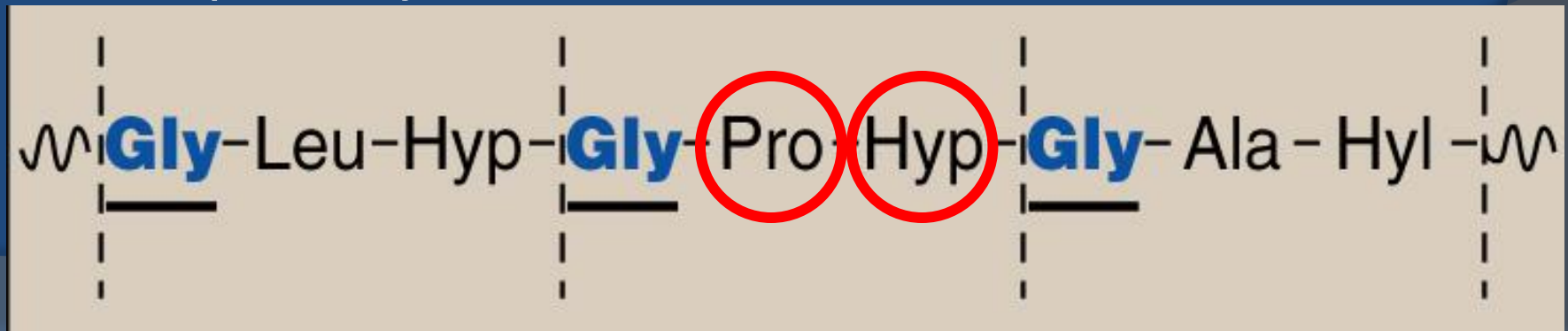




Collagens –STRUCTURE

- In each polypeptide chain, every 3rd amino acid is glycine (Gly), and the sequence of an α-chain can be expressed as (Gly-X-Y)n, where X and Y represent other amino acids and n varies according to the length of the α-chain.

- A high number of proline (Pro) and hydroxyproline (Hyp) residues are in the X and Y positions, respectively



Collagens –STRUCTURE

- Hydrogen bonds between the hydroxyl groups of Hyp contribute to the **stability** of the helix.

Collagens –STRUCTURE

- The prototype collagen (type I) has an **uninterrupted** Gly-X-Y repeat sequence that is almost 1000 amino acid residues in length. This forms a **rigid**, rod-like structure with a diameter of 1.5 nm and length of 300 nm.

Collagens –STRUCTURE

- In some collagens, the (Gly-X-Y)n repeats are **interrupted** by one or more amino acids. The interruptions may be numerous and longer than the (Gly-X-Y)n repeats, and they provide the molecule with **flexibility**, which is important for the specific functions of a given collagen type.

Collagens –BIOSYNTHESIS

SITES:

- Collagens are genetically-distinct and demonstrate considerable tissue specificity. So, they are synthesized by a number of ***different cell types*** including:
  1. epidermal keratinocytes
  2. dermal fibroblasts
  3. vascular endothelial cells
  4. smooth muscle cells

Collagens –BIOSYNTHESIS

STEPS:

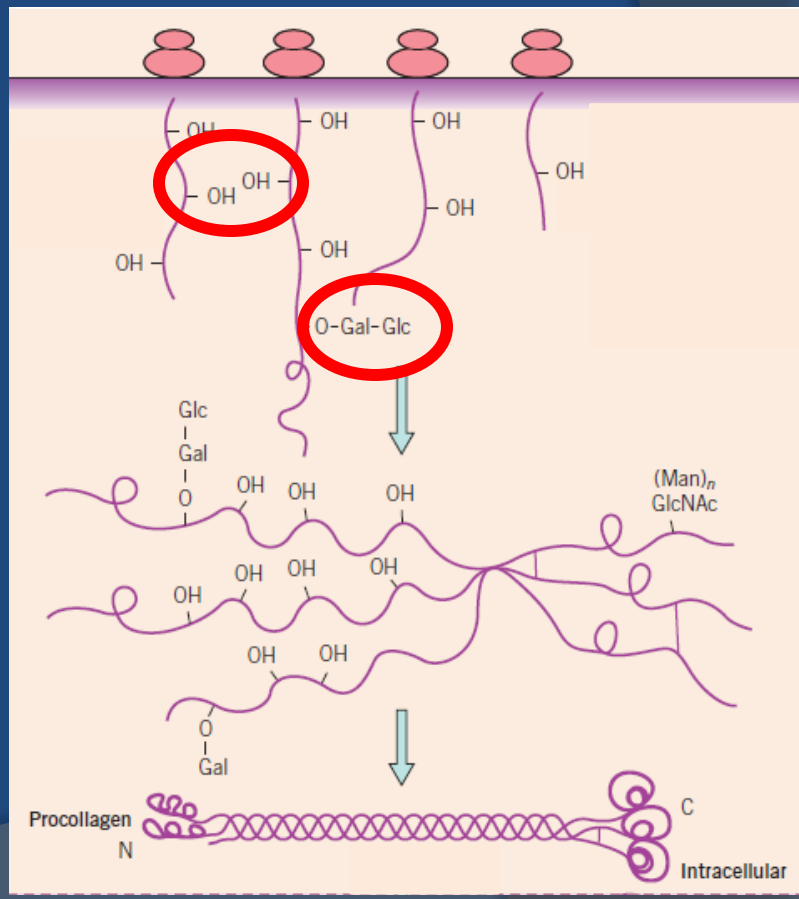
- Collagen biosynthesis involves a number of post-translational modifications

- Some collagens are first synthesized as procollagens that have propeptide extensions at their N-terminus, their C-terminus, or both termini.

Collagens – BIOSYNTHESIS

STEPS: the main intracellular steps in collagen biosynthesis include:

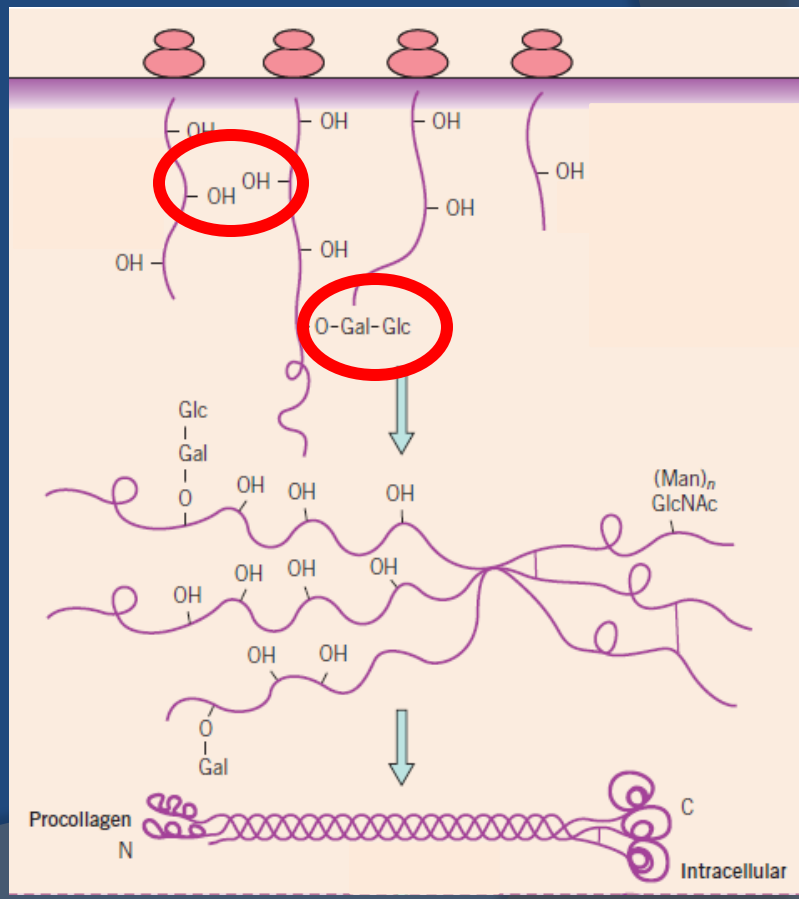
1. cleavage of signal peptides
2. hydroxylation of certain Pro and Lys residues to Hyp and Hyl
3. glycosylation of some Hyl residues to galactosyl-Hyl and glucosylgalactosyl-Hyl
4. glycosylation of certain asparagine residues



Collagens –BIOSYNTHESIS

STEPS:

5. association of the α-chains in a specific manner
6. formation of intra- and intechain disulfide bonds
7. folding of the triple helix



Collagens – BIOSYNTHESIS

Enzymes involved in the biosynthesis of collagens (intracellular):

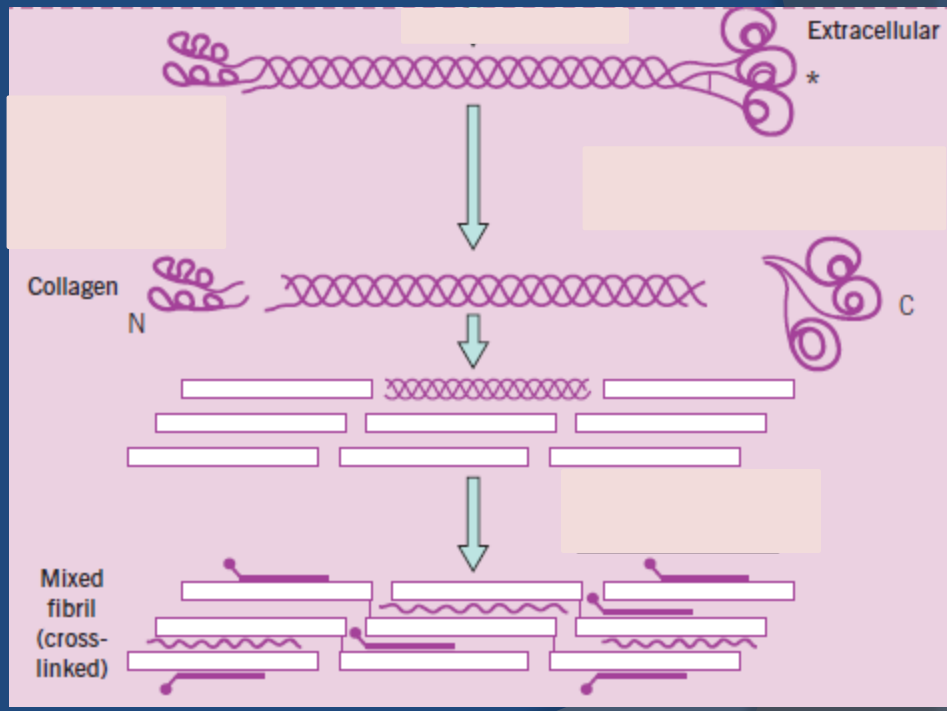
- **prolyl-4-hydroxylase**
- **prolyl-3-hydroxylase**
  - hydroxylate Pro & Lys residues to Hyp, Hyl
  - require O2, Fe2+, α-ketoglutarate and ascorbate (vitamin C) as cofactors
- **Glycosyl-transferases**
  - add glucosylgalactosyl disaccharides onto the α-chains

Collagens –secretion and extra-cellular modification

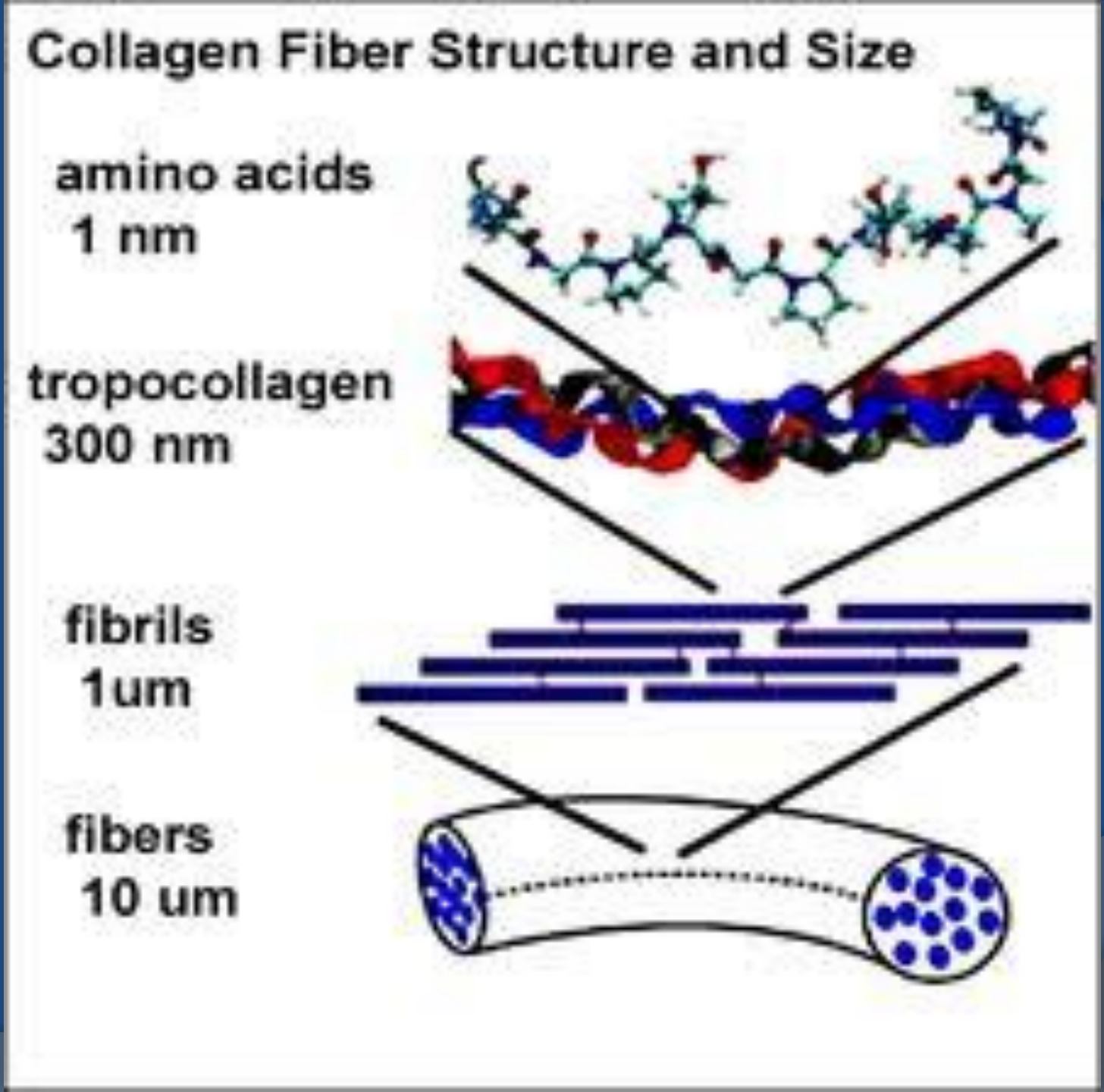
- procollagen molecules are transported from the endoplasmic reticulum to the Golgi apparatus
- during this transport, the molecules begin to aggregate laterally and form early fibrils ready for secretion

Collagens –secretion and extra-cellular modification

- *extracellular steps in biosynthesis:*
  - cleavage of the N- and/or C-terminal propeptides
  - assembly into supra-structures with other collagens and non-collagenous components
  - formation of covalent cross-links



Collagen Fiber Structure and Size



Collagens –BIOSYNTHESIS

extracellular processing enzymes :

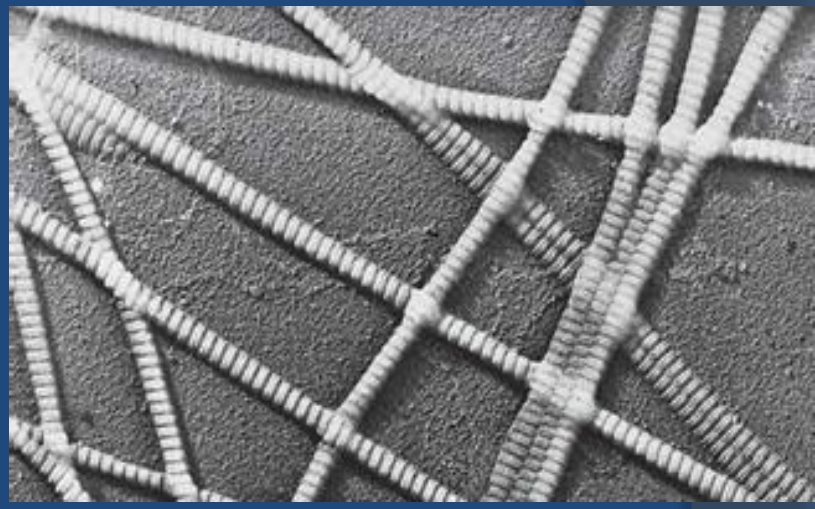
- **Procollagen I N-proteinase:**
  - cleaves the N-propeptide of procollagens I and II
- **Procollagen C-proteinase:**
  - cleaves the C-propeptide of collagens I, II, III, V and VII
- **Lysyl oxidase**
- **Tissue transglutaminase**
  - Cross-linking between collagen molecules

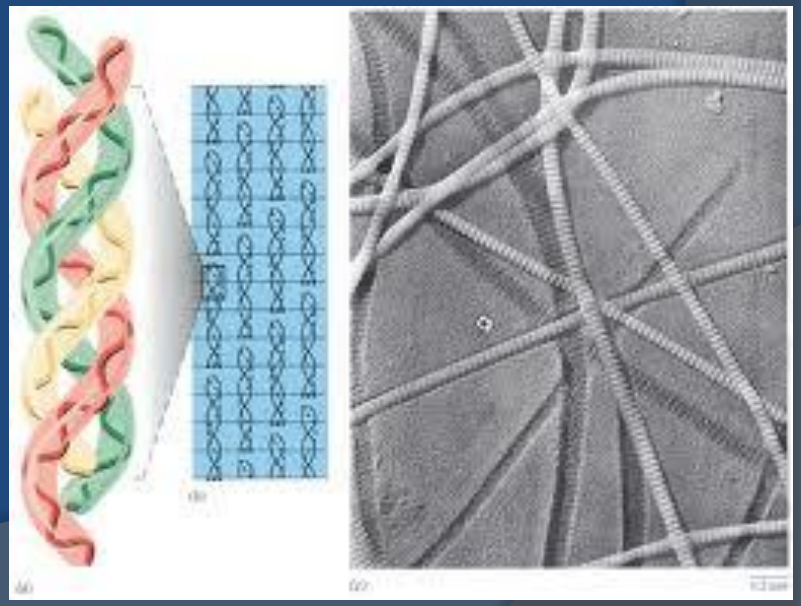
Collagens of the skin

- 75% of the dry weight of the dermis
- 20–30% of the volume of the dermis
- Different collagens polymerize into distinct supra-structures and have specific functions in the dermis as well as in epidermal and vascular basement membranes
- “Pure” collagen fibrils do not exist; they are always mixtures of several collagens and other molecules, e.g. proteoglycans

Collagens of the skin

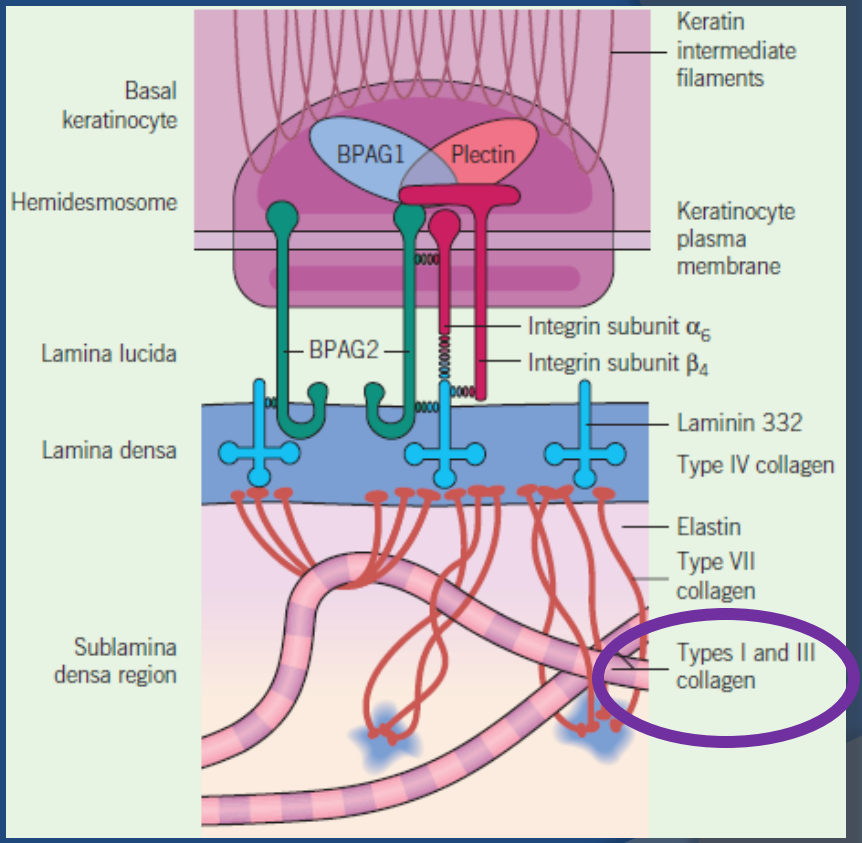
- Classic, ultra-structurally recognizable, cross-banded fibrils in the dermis contain **collagens I, III, V, XII and XIV**
- The characteristic **cross-banding** with periodicity of **64 nm** results from precise lateral packing of the different collagens within the fibrils





Collagens of the skin

- **Type I collagen**
  - the most predominant collagen in human dermis (80%)
- **Type III collagen**
  - about 10% of the total collagen in dermis



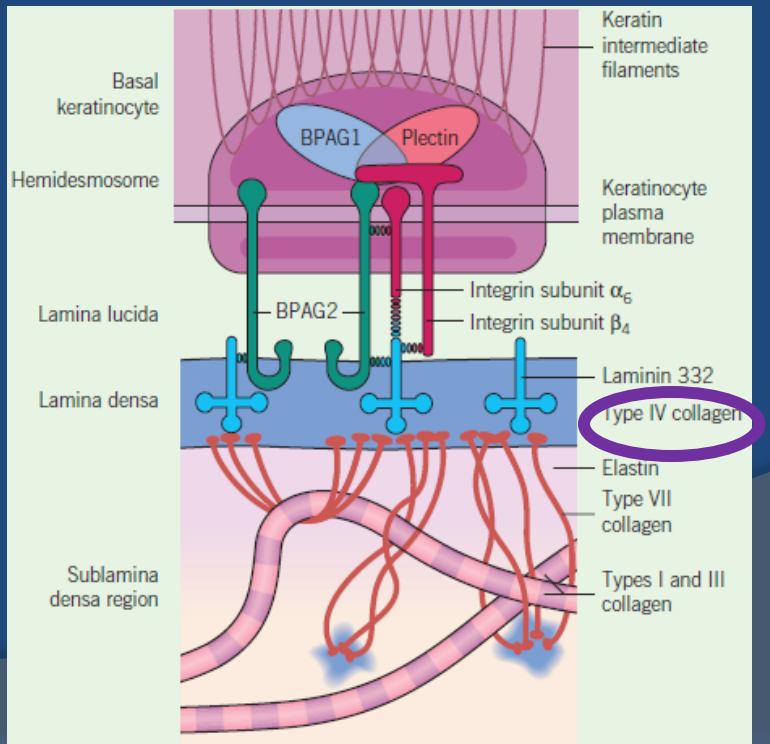
Type I collagen associates with type III collagen to form broad, extracellular fibres in the human dermis

Collagens of the skin

- Mutations in the **type I** collagen gene are responsible for the fragility of bones in **osteogenesis imperfecta**.

- Mutations in **type I and III** collagens, or in their processing enzymes, can result in connective tissue abnormalities in the different forms of **Ehlers–Danlos syndrome**

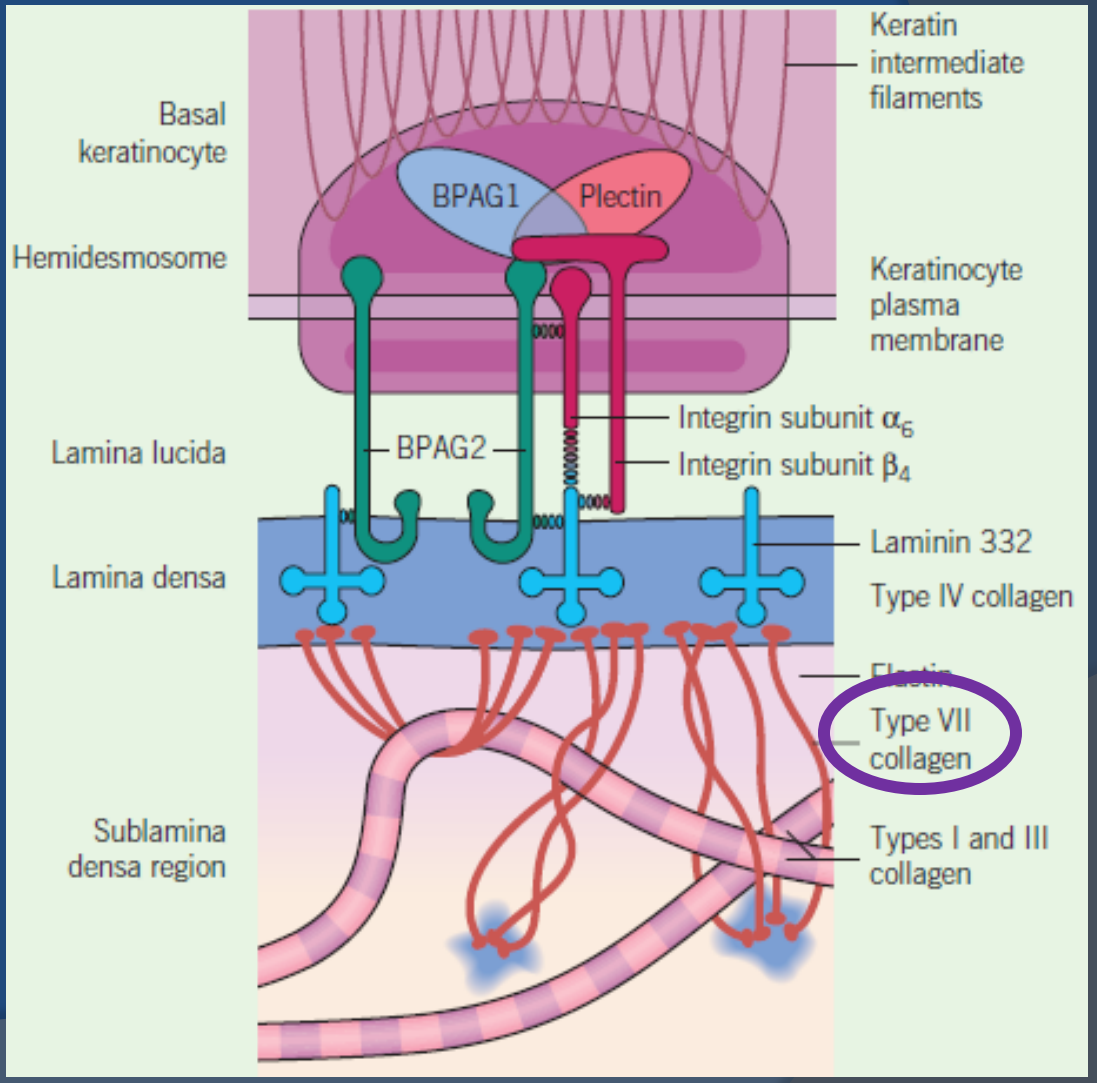
- **Type IV collagen**
  - a basement membrane collagen present within the dermal–epidermal junction as well as in the vascular basement membranes



- **Type V collagen**
  - less than 5% of the total collagen in the dermis
  - located on the surface of large collagen fibres in the dermis, regulate the lateral growth of these fibres contributing to connective tissue stability
  - mutations in the type V collagen gene = Ehlers–Danlos syndrome

- **Type VI collagen**
  - a relatively minor collagen in human dermis
  - assembles into thin microfibrils independent of the broad collagen fibres, which consist primarily of type I and type III collagens
  - Mutations in type VI collagen genes = different forms of muscular dystrophy with little effect on skin physiology

- **Type VII collagen**
  - the major if not the exclusive component of **anchoring fibrils**
  - Mutations = dystrophic epidermolysis bullosa
  - Autoantibodies = EB acquisita



- **Type XVII collagen:**
  - 180-kDa bullous pemphigoid antigen (BPAG2)
  - Autoantibodies =
    - bullous pemphigoid
    - herpes gestationis